memo

JUL 18 1990

to: Paul Goldenheim, M.D.
Richard S. Sackler, M.D.
Michael Friedman

from: Robert F. Kaiko, Ph.D.

dept: Medical

subject: Controlled-Release Oxycodone

date: July 16, 1990

As a follow-up to our meetings regarding the clinical research priorities to which we would like to give this product, I merely document the background and outcome of recent meetings and propose a program for our consideration.

Background:

Oxycodone is a morphine-like opioid agonist analgesic which, on the basis of single-dose, well controlled studies in cancer patients, is thought to be two-thirds as potent as morphine intramuscularly (15mg IM oxycodone is equivalent to 10mg IM morphine) and half as potent orally as intramuscularly (30mg p.o. oxycodone is equivalent to 15mg IM oxycodone). By extrapolation, one might predict that 30mg p.o. oxycodone is equivalent to between 30-60mg p.o. morphine. The time-action of oral oxycodone and morphine are likely to be comparable. Relatively little is known regarding the clinical pharmacology of oxycodone. It is thought to have an elimination half-life which is relatively short and comparable to that of morphine, but a relatively small "first pass" effect such that it is relatively more bioavailable orally as compared to morphine.

In the U.S., oxycodone is utilized most commonly in combination with aspirin or acetaminophen and because of this has an image of being an "earlier stage" analgesic. It is interesting to note, however, that in the State of Connecticut and perhaps other states, the substance abuse officials consider oxycodone combinations among the most abused of Schedule II narcotic analgesic drugs. Dr. William T. Beaver of Georgetown University, in reviewing the clinical pharmacology of combination analgesics, has considered oxycodone a "sleeping giant" in that among all of the opioid analgesics utilized in fixed combinations, oxycodone is the only one with an analgesic potential comparable to that of morphine.

Rationale for Another Controlled-Release Opioid Analgesic:

MS Contin may eventually face such serious generic competition that other controlled-release opioids must be considered. Other pharmaceutical firms are thought to also be developing other controlled-release opioid analgesics.

While averaged data from studies suggest that most morphine-like agonist analgesics are comparable in their relative therapeutic merits, routine clinical practice suggests that some patients just "do better" on particular opioids.

While we are "going laterally" with MS Contin to non-cancer pain indications, it would be unwise to "put all of our eggs into the MS Contin basket" in face of the prospect of generic MS Contin competition that would "crush all of the analgesic eggs".

It has also been said that Purdue Frederick should market in controlled-release formulation every major opioid analgesic and combination analgesic.

Rationale for Controlled-Release Oxycodone in Particular:

Theoretically, oxycodone has an ideal combination of a short elimination half-life and high oral to parenteral bioavailability for a controlled-release opioid analgesic. This combination of characteristics is not shared by any

Trial Exhibit
Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS);
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)
DX 3165

Deposition Exhibit
Purdue et al. v. Endo et al.
Nos. 00 Civ. 8029 (SHS);
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)
DX 326

2/27/02 GCB

other morphine-like agonist analgesic. The shorter the elimination half-life, the sooner steady-state and therefore stable pain control is achievable; the greater the oral to parenteral bioavailability the less intra- and interindividual variation in bioavailability and, thus, the more efficient the titration process and the stabler the stabilization process. While the theoretical argument may be relatively strong using available data, it may be difficult to demonstrate these claims within the context of efficacy studies. Thus, an acceptance of a priority program for controlled-release oxycodone should not assume that all these claims can be demonstrated.

While we have reason to believe that other pharmaceutical firms are formulating controlled-release morphine and controlled-release hydromorphone, there is no evidence to date that this is being done with oxycodone. A controlled-release oxycodone is, thus, less likely to initially have generic competition.

Controlled-release hydromorphone is in formulation and thus there is no choice at this time as to which to give clinical research priority. In addition, some products are particularly difficult to formulate as controlled-release products.

Controlled-release oxycodone with APAP is also in formulation. While this product is thought to be potentially more profitable than controlled-release oxycodone alone, this fixed combination would be limited in the cancer pain market by the very fact that the combination is fixed. Controlled-release oxycodone alone and the controlled-release combination need not necessarily compete with each other.

Studies To Date:

Please refer to the attachments.

Recent Meetings:

A recent meeting with Michael Friedman, Paul Goldenheim and I provided the basis for the proposed positioning of controlled-release oxycodone and for a priority clinical research program. A subsequent with Dr. Richard Sackler and Paul Goldenheim provided a basis for an addition to the clinical research program. Finally, the recent local R & D Meeting provided the basis for refinements of the Phase I research program already conducted.

Positioning:

- Controlled-release oxycodone will be indicated primarily as the opioid analgesic of choice for the management of chronic, moderate to severe cancer-related pain due to its theoretical and, possibly, demonstrable advantages over morphine given that there will be substantial generic MS Contin competition.

- Controlled-release oxycodone may, alternatively, be positioned against fixed combinations of oxycodone (Percocet, Percodan, Tylox) as an unfixed combination with various NSAIDs which can provide for continued pain control in the patient in whom opioid requirements go beyond those provided by the fixed combination analgesics.

- Alternatively, controlled-release oxycodone would be positioned against other short-acting analgesics in patients in whom an acceptable balance cannot be obtained between pain control and adverse reactions with MS Contin.

- Controlled-release oxycodone may also be positioned against numerous analgesics in non-cancer painful indications including chronic non-malignant pain and perioperative uses so as not to (as previously discussed) "crush all of the MS Contin eggs".

Clinical Research Program:

- A steady-state comparative bioavailability study of the new aqueous formulation of the 10mg controlled-release tablet q12h vs. 5mg immediate-release oxycodone q6h; this steady-state study may be preceded by a single-dose phase based on the earlier pilot study so as to definitively establish the single-dose parameters of the controlled-release 10mg tablet as compared to the immediate release oxycodone.

- A definitive study based on the initial pilot to definitively establish the bioequivalency of the 30 and 10mg controlled-release formulations.

- A repeated-dose (approximately one week) relatively well controlled comparison of controlled-release oxycodone q12h vs. IR oxycodone q6h in approximately 200 cancer patients per arm to provide for a total of at least 400 patients. This is the clinical study likely to be of greatest interest to the FDA.

- A "marketing" study of approximately 1-3 months of dosing of controlled-release oxycodone added to NSAIDs in patients uncontrolled on NSAIDs in comparison to patients randomized to receive fixed combinations of oxycodone with acetaminophen or aspirin in order to demonstrate the advantage of the flexible combination over the fixed combinations of oxycodone. We would anticipate that at some point in most patients pain management regimen, the fixed combinations will be required at maximally labeled doses and will eventually be insufficient to control pain and, in these patients, the flexible combination will also be substituted.

- The development of a review paper based on currently available literature which addresses the theoretical argument for controlled-release oxycodone being the ideal controlled-release analgesic for the most efficient management of chronic cancer-related pain.

- A single-dose perioperative study comparing controlled-release oxycodone to placebo administered preoperatively for early postoperative analgesia.

- An evaluation in chronic non-malignant pain under well controlled conditions.

While we intend to review these above issues at the upcoming Medical/Marketing meeting regarding drugs in development, I would appreciate any comments you may have before then.

RFK/mk
Attachments
cc: Tom Compton
Bob Segar
Bob Grandy
Buddy Prettyman
Michael Fanucchi, M.D.

OXYCODONE ACROCONTIN 10MG AND 30MG TABLETS

OC87-0105: (ORGANIC)	SINGLE-DOSE BIOAVAILABILITY 1x30MG VS 3x10MG VS 30MG SOLUTION
OC87-1003: (ORGANIC)	STEADY-STATE BIOAVAILABILITY 10MG TABLET Q12H VS 5MG SOLUTION Q6H
OC87-0501: (AQUEOUS)	10MG TABLET IN FED VS FASTED SUBJECTS
OC88-1105: (AQUEOUS)	RANDOMIZED, DOUBLE-BLINDED, SINGLE DOSE ANALGESIC STUDY IN PATIENTS WITH ABDOMINAL AND GYNECOLOGIC SURGERY
OC89-0702: (BOTH)	COMPARATIVE BIOAVAILABILITY (PILOT) 10MG ORGANIC SOLVENT VS 10MG AQUEOUS SOLVENT

6/90

OC88-1105

"DOUBLE-BLIND, RANDOMIZED, SINGLE DOSE, PARALLEL GROUP STUDY TO ASSESS THE RELATIVE ANALGESIC EFFECTIVENESS AND SAFETY OF GRADED DOSES OF CONTROLLED-RELEASE OXYCODONE COMPARED TO IMMEDIATE RELEASE OXYCODONE, PERCOCET AND PLACEBO IN PATIENTS WITH POSTOPERATIVE PAIN DUE TO ABDOMINAL OR GYNECOLOGICAL SURGERY"

TO DETERMINE THE RELATIVE EFFICACY AND TIME COURSE OF ANALGESIA OF CR OXYCODONE

SINGLE DOSE, DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP ANALGESIC STUDY IN ABDOMINAL SURGERY PATIENTS

CR Oxycodone, 10, 20 and 30mg vs. IR Oxycodone, 15mg, vs. 2 Percocet (5mg Oxycodone plus 325mg acetaminophen each) vs. placebo

Sunshine - Caguas Regional Hospital, Caguas, PR & Carolina Hospital, Carolina, PR

TOTAL PATIENTS:	180	ENROLLED:	110
START:	5/89	COMPLETION:	1/91
FC/SS:	7/91		
PUBLICATIONS:	TBD		
NOTE:	CONFIDENTIAL PRODUCT		

6/90

OC89-0702

"A COMPARATIVE SINGLE DOSE BIOAVAILABILITY STUDY OF 20MG OF CONTROLLED-RELEASE OXYCODONE (10MG TABLETS) (TWO FORMULATIONS) AND OXYCODONE HYDROCHLORIDE SOLUTION 20MG (5MG/ML SOLUTION)"

TO ESTABLISH BIOEQUIVALENCY OF AQUEOUS AND ORGANIC CR OXYCODONE TABLETS

SINGLE DOSE, RANDOMIZED, CROSSOVER BIOAVAILABILITY STUDY IN NORMAL VOLUNTEERS

20MG OXYCODONE AQUEOUS CR VS. ORGANIC CR VS. IR

KISICKI - HARRIS LABS, LINCOLN, NE

TOTAL SUBJECTS:	8	ENROLLED:	8
START:	8/89	COMPLETION:	8/89
FC/SS:	6/90		
PUBLICATIONS:	N/A		

NOTE: CONFIDENTIAL PRODUCT; A FORMULATION STUDY

6/90

OC87-0501

"A SINGLE DOSE, RANDOMIZED, CROSSOVER, BIOAVAILABILITY STUDY OF ONE CONTROLLED-RELEASE OXYCODONE 10MG TABLET IN FED VS. FASTED STATES"

TO DETERMINE THE EFFECT OF A HIGH-FAT MEAL ON CR OXYCODONE BIOAVAILABILITY

SINGLE DOSE, RANDOMIZED, CROSSOVER, BIOAVAILABILITY STUDY IN NORMAL VOLUNTEERS

CR OXYCODONE WITH AND WITHOUT A HIGH-FAT MEAL

HUNT - PHARMACO DYNAMICS RESEARCH, AUSTIN, TX

TOTAL SUBJECTS:	24	ENROLLED:	24
START:	1/89	COMPLETION:	1/89
FC/SS:	6/90		
PUBLICATIONS:	TBD		

NOTE: CONFIDENTIAL PRODUCT; MODEST FOOD EFFECT

6/90

OC87-1003

"STEADY-STATE BIOAVAILABILITY OF ONE CONTROLLED-RELEASE OXYCODONE 10MG TABLET, Q12H, AND 5MG IMMEDIATE RELEASE OXYCODONE HYDROCHLORIDE SOLUTION, Q6H"

TO ESTABLISH THE BIOAVAILABILITY AND CONTROLLED-RELEASE CHARACTERISTICS OF CR OXYCODONE AT STEADY-STATE

REPEATED-DOSE, RANDOMIZED, CROSSOVER BIOAVAILABILITY STUDY IN NORMAL VOLUNTEERS

CR OXYCODONE, 10MG, Q12H VS. IR OXYCODONE 5MG, Q6H

DIXON - HAZELTON LABS, MADISON, WI

TOTAL SUBJECTS:	24	ENROLLED:	22
START:	11/87	COMPLETION:	12/87
FC/SS:	12/89		
PUBLICATIONS:	TBD		

NOTE: CONFIDENTIAL PRODUCT